REMARKS

The Official Action dated February 5, 2008 has been carefully considered. It is believed that the present Amendment places this application in condition for allowance, and reconsideration and an early allowance are respectfully requested.

By the present amendment, claims 21-26 have been added, support for which may be found in the specification, for example at page 10, lines 3-21 and Tables 1 and 2 at pages 22 and 23. It is believed these changes do not involve any introduction of new matter. Accordingly, entry of this Amendment is believed to be in order and is respectfully requested. Claims 9-14 and 18-26 are pending.

In the Official Action, claim 9 was rejected under 35 U.S.C. §103 as being obvious and unpatentable over the Kroeger et al U.S. Patent Publication No. 2002/0137021 in view of the Gissmann et al U.S. Patent No. 6,228,368, the Goldsborough et al GenBank Accession No. J04353, Seedorf et al, *EMBO J.* (1987), Sastre-Garau et al, *J. Gen. Virol.* (2000), the Sastre-Garau et al GenBank Accession No. AJ242956, and Buck et al, *Biotechniques* (1999). The Examiner asserted that Kroeger et al teach a kit for detecting oncogenic HPV, including HPV 16, 18, 31 and 45, comprising primers and probes that could be used in a cocktail for amplification and detection of multiple HPV types at once. The Examiner further asserted it would have been "obvious to try" the sequences taught by Gissmann, Goldsborough, Seedorf and Sastre-Garau to design amplification primers and probes for a kit to detect and quantify HPV in a type-specific manner as taught by Kroeger et al, relying on *KSR International Co. v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007). The Examiner relied on Buck et al as evidencing the equivalence of primers.

Claims 10 and 11 were rejected under 35 U.S.C. §103 over the aforementioned references and in further view of Yoo et al, *Genomics* (1993), which the Examiner asserted as teaching a sequence that can be used for designing primers of SEQ ID NOS: 19 and 20 and

the probe of SEQ ID NO: 30. Claims 12 and 14 were rejected under 35 U.S.C. §103 over the aforementioned references and in further view of Swan et al, *J. Clin. Microbio.* (1997), which the Examiner asserted as teaching type-specific fluorogenic probe assays for detection and quantification of HPV. Finally, claims 13 and 18-20 were rejected under 35 U.S.C. §103 over the aforementioned references and in further view of Swan, the Examiner again relying on Swan's fluorogenic probe assays.

These rejections are traversed and reconsideration is respectfully requested. None of the combinations of cited references teach or suggest a kit as defined by any of claims 9-14 and 18-20, or the improvements provided thereby for detection and quantification of human papillomavirus (HPV).

More particularly, as defined by independent claim 9, the present invention is directed to a kit for detection and quantification of human papillomavirus (HPV). The kit comprises a) the amplification primers SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5/SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8, and the probes SEQ ID NO:21, SEQ ID NO:22 and SEQ ID NO:23/SEQ ID NO:24, for HPV 16, 31, 18, 45; and optionally b) the amplification primers SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13/SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16 and SEQ ID NO:17/SEQ ID NO:18 and the probes SEQ ID NO:25, SEQ ID NO:26 and SEQ ID NO:27/SEQ ID NO:28/SEQ ID NO:29 for HPV 33, 35, 39, 52, and 58.

As described in the present specification, for example at page 2, beginning at line 24, the kit of the present invention has the advantage of detecting and quantifying the HPV types most commonly detected in cervical tumors, while, importantly, minimizing the number of parallel reactions performed for each sample, making the system suitable for use in routine screening of cervical swab samples. Further, as described in the specification, for example at page 3, line 8, the probes are selected so as not to compete during amplification-reaction and

detection. Particularly, the Examiner's attention is directed to the present specification at page 10, beginning at line 14, which discloses that the primers and probes in the kit of claim 9 are selected and combined to optimize the ability for balanced, co-amplification of different HPV types in a mixed sample and to avoid hindrances to an efficient PCR. Specifically, the amplicon for HPV 16 is located in E7, that for HPV 18/45 in E1, and that for HPV 31 in E6. The amplicons for HPV 33, 52 and 58, HPV 39 and HPV 35 are respectively located in L1, E7 and E4. Accordingly, the defined kit optimizes the ability for balanced co-amplification. As described in detail at pages 17-20 of the present application, the kit of claim 9 makes it possible to quantitatively analyze multiple types of HPV, or groups of HPV, in one reaction vessel by providing the claimed combination of primers which do not compete during amplification. New claims 21-26 incorporate this feature as well. The kits of the invention therefore provide a significant advantage in the ability to quantify individual HPV types in mixed infections.

While Kroeger et al disclose probe sequences useful for detecting oncogenic HPV types in a test sample, and particularly a cocktail of probes, as noted by the Examiner, the sequences employed by Kroeger et al are significantly different from the primers and probes required by claim 9. Specifically, Kroeger et al teach that all of the probes (i.e., oligonucleotides or oligos) can be employed as primers in an amplification reaction but preferably are employed as hybridization probes because each probe is specific for at least one HPV or two HPV types. Kroeger et al additionally teach that all of the probes hybridize within an approximately 140 bp region of the L1 gene found in the HPV genome; thus, while the probes individually can be used to detect the oncogenic HPV type(s) for which they are specific, a cocktail comprising two or more of the oligos can be employed to detect several HPV types at once (paragraph [0007]). Thus, Kroeger et al do not teach or suggest the

optimization for balanced co-amplification provided by the kits of the present invention, achieved by amplification in different HPV reading frames.

Each of the secondary references cited in the rejections respectively discloses a specific primer or probe or a combination thereof. However, none of these references teach the combination of primers of SEQ ID NOS: 1-8 and probes of SEQ ID NOS: 21-24 as required by claim 9, or, importantly, that such a combination of primers and probes may be employed in a single kit to quantitatively analyze multiple types of HPV, or groups of HPV, in one reaction vessel, without competition among the primers during amplification. In fact, Buck et al teach away from such a combination and demonstrate the nonobviousness of the presently claimed kit as Buck et teach that every primer would be suitable. However, Buck et al are only interested in amplification of a test nucleic acid. On the other hand, the kit of the present invention allows a primer pair to amplify a specific nucleic acid while, at the same time, not amplifying a very similar nucleic acid. There is no teaching, suggestion, or motivation in any of the cited references to provide the specific combination of primers recited in claim 9, particularly to obtain this functionality.

The Examiner relied on the Supreme Court's decision in *KSR International Co. v. Teleflex, Inc.*, *supra*, to assert it would have been obvious to try the asserted combinations of primers and probes. However, in *KSR*, the Supreme Court indicated that the instance in which a combination which is obvious to try might show an invention was obvious under §103 is when there are "a finite number of identified, predictable solutions" to a design need or market pressure, *supra* at 1742. That is not the case with the present combination of references as Kroeger et al themselves, along with the various secondary references, show there are numerous oligonucleotides that can be used in combination without achieving the benefits of the present invention.

Moreover, as also noted by the Supreme Court in *KSR*, in determining patentability under 35 U.S.C. §103, it is necessary to determine whether there was an apparent reason to combine the known elements in the fashion of the claim at issue, *KSR International Co. v. Teleflex, Inc.*, *supra* at 1740-41. None of the cited references provide any apparent reason to combine their teachings in a single kit as presently claimed, particularly with the ability to analyze multiple types of HPV, or groups of HPV, in one reaction vessel, without competition among the primers during amplification. Accordingly, the kits defined by claim 9, and claims 10-14 and 18-20 dependent thereon, are nonobvious over and patentably distinguishable from the cited combinations of references.

Finally, in the Official Action, the Examiner asserted that the absence of competition among the primers during amplification represents an intended use and does not carry weight for examination of the product claims. Applicants respectfully disagree. That is, it is well settled that evidence sufficient to rebut an obviousness rejection may comprise evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art, MPEP Section 2145. The present kits allow quantitative analysis of multiple HPV types, which has not been shown to be present in the prior art. The Examiner cannot ignore the unobvious advantages provided by the combination of primers and probes as claimed. When these advantages are properly considered, it is apparent that the claimed kits are patentably distinguished from the cited combinations of references.

Accordingly, the rejections under 35 U.S.C. §103 have been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the Official Action and places the present application in condition for allowance. Reconsideration and an early allowance are requested. In the event that there are any outstanding issues in the present

application, the Examiner is encouraged to contact the undersigned to discuss the same in order to further expedite prosecution.

Please charge any fees required in connection with the present communication, or credit any overpayment, to Deposit Account No. 503915.

Respectfully submitted,

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